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EXAMINER	
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ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/887,540	KLEIN, ROBERT	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 January 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,13-21,24 and 26-31* is/are pending in the application.

4a) Of the above claim(s) *1-4,13-16,20,21 and 31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-19,24 and 26-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 5-12, 20-23 and 25 remain cancelled. Applicants response filed 1-28-05 continues to fail to list claims 20 and 21 as being canceled. However, claims 20 and 21 were canceled in the response filed 2-27-04.

Claims 26-31 have been added.

Claims 1-4, 13-19, 24 and 26-31 are pending.

This application contains claims 1-4 and 13-16 drawn to an invention nonelected with traverse in Paper No. 10. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claim 31 is withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention of Group V in the restriction requirement sent 10-2-02, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 11-12-02.

Claims 17-19, 24 and 26-30 are under consideration in the instant office action. Claims 20 and 21, listed by applicants as pending, are not under consideration in the instant office action because they were canceled on 2-27-04.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Applicant's arguments filed 1-28-05 have been fully considered but they are not persuasive.

The term "LPR5" in new claim 26 and throughout the claims should be "LRP5" (see specification on pg 2, line 18).

Specification

The amendment filed 1-28-05 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows:

The addition of the application numbers into paragraph 1 of pg 10 is new matter. No support for the patent applications is found in the specification as originally filed. Deletion of application 08/971310 in paragraph 1 of pg 10 as teaching methods of preparing a targeting construct from a plasmid genomic library is also new matter.

Applicant is required to cancel the new matter in the reply to this Office Action.

The application number in pg 10, paragraph 2, must be updated upon being allowed.

Claim Rejections - 35 USC § 101

Claims 17-19 and 24 remain rejected and claims 26-30 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific or substantial asserted utility or a well-established utility for reasons of record.

Claims 17-19 and 26-30 are directed toward a transgenic mouse whose genome comprises a null endogenous low density lipoprotein related protein 5 (LRP5) allele, said allele comprising exogenous DNA.

REVISED INTERIM UTILITY GUIDELINES TRAINING MATERIALS repeated from http://www.uspto.gov/web/menu/utility.pdf

"Specific Utility" - A utility that is specific to the subject matter claimed. This contrasts with a general utility that would be applicable to the broad class of the invention. For example, a claim to a polynucleotide whose use is disclosed simply as a "gene probe" or "chromosome marker" would not be considered to be specific in the absence of a disclosure of a specific DNA target. Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.

"Substantial utility" - a utility that defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. For example, both a therapeutic method of treating a known or newly discovered disease and an assay method for identifying compounds that themselves have a "substantial utility" define a "real world" context of use. An assay that measures the presence of a material, which has a stated correlation to a predisposition to the onset of a particular disease condition, would also define a "real world" context of use in identifying potential candidates for preventive measures or further monitoring. On the other hand, the following are examples of situations that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use and, therefore, do not define "substantial utilities":

A. Basic research such as studying the properties of the claimed product itself or the mechanisms in which the material is involved.

B. A method of treating an unspecified disease or condition. (Note, this is in contrast to the general rule that treatments of specific diseases or conditions meet the criteria of 35 U.S.C. 101.)

C. A Method of assaying for or identifying a material that itself has no "specific and/or substantial utility".

D. A method of making a material that itself has no specific, substantial, and credible utility.

E. A claim to an intermediate product for use in making a final product that has no specific, substantial, and credible utility.

(Page 5-7 of utility guidelines).

A "well-known utility" is a specific, substantial and credible utility which is well know, immediately apparent, or implied by the specification's disclosure of the properties of the material, alone or taken with the knowledge of one skilled in the art. Neither a "well-established utility" nor a "specific utility" applies to any

> utility that one can dream up for an invention or a utility that would apply to virtually every member of a general class of materials, such as proteins or DNA.
>
> (Paragraph bridging pg 32-33 of utility guidelines).

Using a knockout mouse to determine the function of a gene is not a substantial utility because the phenotype of mouse is not necessarily reflective of the knocked out gene. Olsen of record (GABA in the Nervous System, 2000, pg 81-95) taught that "although gene targeting is often useful in delineating the contribution of a given gene product to phenotypic characteristics observed, some gene knockouts lead to embryonic or perinatal lethality, and others lead to no apparent phenotype. This can arise from a lack of any role for the gene in question in regard to the trait studies or from compensation by other gene products. Analysis of the compensation can yield valuable clues to the genetic pathway" (pg 82, last 11 lines of col. 1). Thus, knockout mice may not be capable of elucidating the function of the protein and may only provide a clue to a pathway the protein being knocked out is involved in. Using mice to obtain a clue to a pathway is not a "substantial utility." Therefore, using a mouse with a phenotype that may have been caused by genes compensating for the knocked out gene is not a "specific utility" because the phenotype is not specific to the knocked out gene.

Using the mice to identify agents capable of altering a phenotype would require further research and is not a "substantial utility" or "specific utility." Bowery of record (Pharm. Rev., 2002, Vol. 54, pg 247-264) taught, "no unique

pharmacological or functional properties have been assigned to either subunit or the variants" of $GABA_B$. "The emergence of high-affinity antagonists for $GABA_B$ receptors has enabled a synaptic role to be established. However, than antagonists have generally failed to establish the existence of pharmacologically distinct receptor types within the $GABA_B$ receptor class. The advent of $GABA_{B1}$ knockout mice has also failed to provide support for multiple receptor types" (pg 247, col. 2, lines 4-). Thus, knockout mice may be used to identify agents that bind to the knocked out gene ($GABA_B$ in the case of Bowery or lipoprotein-related protein 5 in the instant application), but the agent may not treat disease or ameliorate any symptom of disease. Further research would be required to determine how to use such an agent identified using the mouse, which is not a "substantial utility" (see Utility Guidelines for examples of things that do not have "substantial utility" "C. A Method of assaying for or identifying a material that itself has no "specific and/or substantial utility"). Using the mice to identify agents capable of altering a phenotype is also not a "specific utility" because the agent may be affecting other proteins in the pathway and not LPR5 itself. Using the mice to identify agents capable of altering a phenotype is also not a "specific utility" because the agent may be found using wild-type mice.

Olsen and Bowery also show that knockout mice do not necessarily reveal the function of the knocked out gene. Neither reference used the mice to determine the function of the knocked out gene. Significant further research would be required to do

so because no blaze marks for determining the genes' function using the mice have been set forth.

The specification teaches making LRP5 -/- mice (pg 50). The specification suggests using the mice to test compounds for neurological, neuropsychological or psychotic disease, but the specification does not disclose one specific neurological, neuropsychological or psychotic disease in humans linked to a disruption in LRP5 (pg 19, lines 8-11). The mice were tested in "open field testing" (Fig. 4 and 5 and pg 51); however, the results of the open field test do not correlate to a useful phenotype because "possible increased anxiety" and "significant hypoactivity" (lines 4 and 7 of pg 51) are not specific to any disease and are not statistically significant because the number of mice tested is not disclosed and the difference observed is not significant. In fact, it cannot be determined what the "2,1," means in "2,1, -/-, Male" or "2,1, +/+, Male" in Fig. 4 and 5. The mice also had retinal degeneration. The specification suggests using the mice as a model of disease relating to disruptions in LRP5 (pg 19, lines 4-6). However, retinal degeneration has not been linked to the LRP5 gene in humans. The mice claimed cannot be used to determine compounds that modulate LRP5 expression because LRP5 is not expressed in the mice. Using the mice to determining whether a particular phenotype is ameliorated is not a specific or substantial utility because the specification does not link the phenotype to any specific disease or to a disease caused by a disruption in humans. The specification does not identify any compounds that alter neurological, neuropsychological, or psychotic phenotypes using the mice. Thus, the

specification does not provide a specific or substantial use for a mouse having retinal degeneration, increased anxiety or hypoactivity as claimed.

Significant further research would be required to use the mice to determine the function of the LRP5 gene because applicants have not set forth any blaze marks for determining the genes' function using the mice. Applicants have tested the mice in assays but did not determine the function of the LRP5 gene. Nowhere does the specification provide any blaze marks for one of skill in the art to determine the function of the LRP5 gene using the mice. In fact, the mice may never reveal the function of LRP5. Therefore, the mice do not have utility for determining the function of LRP5.

Since the time of filing, LRP5 disruptions have been linked to osteoporosis-pseudoglioma syndrome (OPPG) in humans (Gong of record, 11-16-01, Cell, Vol. 107, pg 513-523, abstract), which is not taught or suggested in the instant application. A mouse having a homozygous disruption in LRP5 having features of osteoporosis-pseudoglioma syndrome has been made since the time of filing (Kato, of record, J. Cell Biology, 2002, Vol.1 57, pg 303-314; abstract and pg 304, col. 2, "Generation of Lrp5-/- mice"), which is not taught or suggested in the instant application. Thus, the specification does not provide the essential blaze marks for one of skill to determine how the mice are linked to human disease.

It was well known that knockout mice could be used for scientific research to determine the function of a gene. However, scientific research is not the same as "patentable utility" or a "well-established" utility.

The MPEP and utility guidelines clearly set forth that a "well-established utility" must be specific, substantial and credible. While knockout mice were used for scientific research in the art at the time of filing, significant further research was required to determine the function of the gene. In fact, the function of the gene may never be determined from the knockout mouse. A mouse requiring significant further research to determine the function of the gene does not rise to the level of having a "well-established utility." Using the mouse for further research is not a substantial utility, which is specifically described in the utility guidelines:

> [T]he following are examples of situations that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use and, therefore, do not define "substantial utilities":
>
> A. Basic research such as studying the properties of the claimed product itself or the mechanisms in which the material is involved.

In this case, further study of mice would have been required to determine how to use the mouse of applicants' invention as a model of disease. The overall phenotype of the applicants' mice does not correlate to any disorder. Therefore, further study would be required to determine how to use the mice as a model for any disease. As such, using the mice claimed to determine whether the mice are a model of disease is not a "substantial utility."

Specifically, claim 17 requires the mouse has hypoactivity. A mouse having hypoactivity as claimed does not have a patentable utility because:

i) Hypoactivity is defined as abnormally decreased motor and cognitive activity, with slowing of thought, speech and movement. Hypoactivity is generic to numerous medical conditions, such as depression and aging. While hypoactivity can be a symptom of a medical condition, hypoactivity can be secondary to medical conditions, i.e. recovery from surgery, the flu, allergies, or can be a symptom of non-medical conditions, i.e. changing jobs from being a construction worker to working behind a desk, laziness, driving to work instead of walking. A mouse that is slower than average in an open filed test does not represent all types of hypoactivity or one particular type of hypoactivity;

ii) Applicants' conclusion in the Example, that a mouse that has a slower velocity represents hypoactivity in an open field test, is unfounded. Applicants' conclusion does not take into account possible physiological conditions that may have caused the slower velocity related to bone or muscle structure/function. Mice having a slow velocity do not correlate directly to all forms of hypoactivity. Mice with a slower velocity than wild-type mice are slower than wild-type mice; that is all that can be concluded from such a study.

iii) Using a mouse having hypoactivity to determine drugs that increase activity is not a specific or substantial utility because wild-type animals can also be used to determine drugs that increase activity.

Applicants argue the claimed invention has a well-established utility because a person of ordinary skill would immediately appreciate why the knockout mice were useful to define the function and role of the disrupted gene. Applicants' argument is not

persuasive.

MPEP 2701 II(A)(3) requires a "well-established utility" must be a utility that is specific, substantial and credible. While knockout mice were used for scientific research in the art at the time of filing, significant further research was required to determine the function of the gene using the mouse. In fact, the function of the gene may never be determined from the knockout mouse. Olsen of record (GABA in the Nervous System, 2000, pg 81-95) taught that "although gene targeting is often useful in delineating the contribution of a given gene product to phenotypic characteristics observed, some gene knockouts lead to embryonic or perinatal lethality, and others lead to no apparent phenotype. This can arise from a lack of any role for the gene in question in regard to the trait studies or from compensation by other gene products. Analysis of the compensation can yield valuable clues to the genetic pathway" (pg 82, last 11 lines of col. 1). A mouse requiring significant further research to determine the function of the gene does not rise to the level of having a "well-established utility" (see utility guidelines, "[T]he following are examples of situations that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use and, therefore, do not define "substantial utilities": A. Basic research such as studying the properties of the claimed product itself or the mechanisms in which the material is involved"). In this case, the results of such further study may never reveal the function of the LRP5 gene and least significant further study would have been required to use the knockout mice to determine the function of the LRP5 gene.

Applicants point to an NIH report from 2004, Austin (Nature Genetics, 2004, Vol.

36, No. 9, pg 921-924), The Molecular Biology of the Cell (Albert, 4th ed., Garland Science (2002)), Gene VII (Lewin, Oxford University Press (2000)), Joyner (Gene Targeting: A Practical Approach, Oxford University Press, 2000), Matise (Production of targeted embryonic stem cell clones in Joyner) and Crawley (What's wrong with my mouse, Behavioral phenotyping of transgenic and knockout mice, Wiley-Liss, 2000) to establish the mice had "well-established" utility (pg 9-12 of response). Applicants' arguments are not persuasive.

First, the NIH report and Austin were not available until 2004 and cannot be used to establish what was "well-established" at the time of filing.

Second, while the NIH report suggests knockout mice may be models of disease, one mouse with lipoma or mice with increased pain sensitivity as claimed are not models of any disease because they are not symptoms of disease.

Lastly, the references merely suggest using knockout mice to study the function of targeted genes, which does not rise to the level of a substantial utility according to the utility guidelines. The NIH report states knockout mice can be used to elucidate gene function. Austin states null-reporter alleles should be created as a starting point for studying the function of every gene. The Molecular Biology of the Cell states mutant mice can be an invaluable tool for investigating gene function. Gene VII states knockout mice are used to investigate directly the importance and function of a gene. Joyner states gene targeting in ES is used to study gene function in a mammalian organism. Matise states knockout ES cells can be used to study gene function in cell culture and in vivo. Crawley states knockout mutations provide a means for

understanding gene function. None of references teach the mice will determine the function of the gene. Applicants have used the mice in expression analysis and phenotype analysis tests, but applicants have not determined the function of the gene. Simply using the mice for further research of the LRP5 gene is not a specific or substantial utility. None of the references teach a specific or substantial utility for mice with a disruption in the LRP5 gene as claimed.

Applicants argue the 103 contradicts the utility rejection (¶ bridging pg 11-12 of response). Applicants' argument is not persuasive. The examiner has provided adequate reasoning to support both the 101 and 103 rejections. The desire of those of ordinary skill to gain clues as to the function of genes was well established at the time of filing. The fact that those of ordinary skill in the art desired to make knockout mice to gain clues as to the function of genes does not necessarily mean the mice would have a specific and substantial utility, i.e. that those of ordinary skill would determine the function of the gene from the clues provided by the mice. Evidence that the mice made may not provide a desired function is provided by applicants who used the mice in various tests and gained clues regarding the gene but did not teach the function of the gene. One of skill may desire to make the mouse without gaining any patentably useful information from the mouse.

Applicants cite en re Brana and state the PTO has the initial burden of challenging the asserted utility in the disclosure for mice with the phenotype described (pg 12). Applicants cite Austin (cited above) and Doetschman (Lab. Animal Sci., 1999, Vol. 49, pg 137-143) who teach mice have much in common with humans and that

knockouts will provide "information concerning gene function..." (pg 14 of response). Applicants' arguments are not persuasive. Only claims 17-19 are limited to mice with a phenotype. Mice with hypoactivity in claims 17 and 19 do not correlate to any diseases. It is not clear that a disruption in LRP5 caused retinal degeneration or anxiety or that humans with retinal degeneration or anxiety have a disruption the LRP5 gene. The examiner has provided ample reasoning and evidence why those of skill in the art at the time of filing would doubt why each phenotype fails to have substantial utility. The examiner has provided ample reasoning why each asserted utility fails to have substantial and/or specific utility. Even applicants' own further research, i.e. the expression, physical and behavioral analysis did not reveal the function of the LRP5 gene. Significant further research in this case is required to use the mice with the phenotypes described to determine the function of the LRP5 gene. Therefore, using the mice with the phenotypes described to determine clues to the function of the LRP5 gene does not constitute a patentable utility.

Applicants are reminded that In re Schoenwald, 22 USPQ2d 1671 (CA FC 1992) indicated that a product known in the art did not necessarily have patentable utility. In this case, the mouse claimed might only provide a clue to a developmental process or signal transduction pathway in which SEQ ID NO:1 is involved. This is not a specific utility because results from the tests may only indicate SEQ ID NO:1 is involved in development or signal transduction pathway. The phenotype provides only a clue that SEQ ID NO:1 is generically involved in development or a signal transduction pathway influenced by

numerous proteins.

Applicants state Crawley taught the open field test was a standard test for evaluating anxiety in Table 10.1 (¶ bridging pg 14-15 of response). Applicants' argument is moot because Table 10.1 has not been provided. Furthermore, the portion of Crawley provided in the exhibits does not state knockout mice displaying decreased time in the central region in an open field test as described in the specification are models of human anxiety.

Applicants argue the results of the open field test were statistically significant because 10 homozygous mice were compared with 10 wild-type controls. Applicants' argument is not persuasive. Nowhere does the specification disclose that ten of each mice were tested. Nor does the specification reveal the type of wild-type control. The knockout used in the test is of mixed strains, and the ES cell strain (129/OlaHsd) used to make the mice may have caused the phenotype observed in the knockout mice as compared to the donor strain (C57Bl6). Crabbe taught C57Bl/6 mice have different phenotypes than other strains of mice (Science, June 4, 1999, Vol. 284, pg 1670-1672). Therefore, a mixed strain knockout mouse as described in the specification may have a phenotype that is found in the contributing ES cell strain (129/OlaHsd) and not in the wild-type C57Bl6 mouse. The specification does not describe comparing the knockout mice with equivalently backcrossed control mice. The mixed strain knockout mouse used in the test was not adequately backcrossed to be properly compared to a wild-type C57Bl6 mouse. 25% of the genome of the mixed strain F2 knockout mouse described in Example 1 of the instant application is from the contributing ES cell strain. The

specification does not teach the mixed strain knockout mouse was backcrossed adequately for a proper comparison to a wild-type C57Bl6 mouse. The specification does not teach that both wild-type C57Bl/6 and the wild-type contributing ES cell strain had the same body weight. As such, one of skill would not be able to conclude that the observed difference was attributed to the knockout of LRP5 and not the 129/OlaHsd genotype of the ES cell strain contributing to the genome of the F2 mice. Thus, the mice claimed do not have substantial utility because the data provided is not substantial.

Applicants argue the knockout mice claimed can be used to predict and understand the gene function in humans, which is a well-known utility (pg 15 of response). Applicants' argument is a reiteration of the arguments above and is not persuasive. The knockout mice may never reveal the function of the gene. Predicting a gene function without teaching the gene function is not substantial because the prediction may not be correct because the blaze marks to determine the function of the gene have not been set forth.

Applicants argue LRP5 has been linked to retinal and eye disorders (Jiao, Am. J. Human Gen., 2004, Vol. 75, No. 5, pg 878-884). Applicants' argument is not persuasive. Jiao was not available at the time of filing. The specification does not provide the blaze marks for one of skill to determine that familial exudative vitreoretinopathy (FEVR) described by Jiao was linked to a disruption in the LRP5 gene using the mice described in the specification.

Applicants argue Gong and Kato of record support "Applicant's original findings" (pg 15 of response 6 lines from the bottom). Applicant's argument is not persuasive. The specification does not provide the essential blaze marks for one of skill to determine LRP5 disruptions were linked to osteoporosis-pseudoglioma syndrome or FEVR found in humans. The assertion that the mice described in the specification would be models of disease would not have been considered credible by a person of ordinary skill in the art at the time of filing because no diseases were linked to a disruption of the LRP5 gene at the time of filing. Significant further research would have been required for one of skill to determine which human disease conditions, if any, were linked to a disruption of the LRP5 gene.

Applicants argue Olsen is irrelevant because the specification must be taken as truthful. Therefore, applicants conclude the examiner's position that the phenotype does not necessarily correlate to a disruption in the knocked out gene is based on conjecture and not fact (¶ bridging pg 17-18 of response). Applicants' argument is not persuasive. Olsen provides evidence of the phenomenon that a phenotype may be caused by genes compensating for a knockout and not necessarily a direct result of the knockout. The examiner has provided a scientific argument based on the teachings of Olsen indicating the phenotype observed in the instant invention may be a result of other proteins in the pathway compensating for the knocked out gene. Merely aiding the understanding of GABA as described by Olsen on pg 91 is not a substantial utility (and was not available at the time of filing. Olsen described mice with a disruption

showed the gene was generic to neurodevelopment, synaptogenesis, and possibly human disease, which is neither specific nor substantial. Applicants have provided no evidence to the contrary that the observed phenotype is a result of the knocked out gene and not of proteins in the same pathway compensating for the knocked out gene.

Applicants argue Bowery fails to support the examiner's position because Bowery provides utility for the mice claimed. "Bowery discusses use of hot-plate, tail-flick and paw pressure protocols to evaluate acute pain behavior in GABA-B 1 null mutant mice. Based on the reported data, Bowery concludes 'it is likely that GABA-B-mediated effects do indeed exert a tonic control of nociceptive processes in the naïve animal" (p. 255, col.2). Thus, applicants conclude Bowery supports the utility of knockout mice in evaluating the role of GABA genes" (pg 18). Applicants' arguments are not persuasive. First, Bowery was not available at the time of filing and cannot establish the utility of mice used in hot plate tests. More importantly, Bowery shows that despite clues gained using knockout mice in hot plate tests, "no unique pharmacological or functional properties have been assigned to either subunit or the variants" of $GABA_B$. Mice that merely provide clues to the gene without teaching the function of the gene do not have a substantial utility.

Applicants argue Mombereau used knockout mice, therefore, applicants conclude the knockout mice had patentable utility (pg 19). Applicants' argument is not persuasive. Scientific utility is not the same as patentable utility. Mombereau was also not available at the time of filing to establish utility. Finally, Mombereau did not discover any drugs capable of treating disease in humans using the mice.

Applicants argue the fact that further research to use the mice to identify drugs capable of treating disease is irrelevant. Applicants' argument is not unfounded and ignores the fact that patentable utility requires that one of skill successfully use the product for its asserted utility. In this case, no blaze marks have been provided by applicants so that the mice could successfully used to identify drugs capable of treating disease giving the art which taught knockout mice may given drugs without identifying drugs capable of treating disease.

Claim Rejections - 35 USC § 112

Enablement

Claims 17-19 and 24 remain rejected and claims 27-30 are rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use mice having retinal degeneration, increased anxiety or hypoactivity for reasons of record.

Applicants argue the claimed invention is enabled for reasons set forth above. Applicants' argument is not persuasive for reasons set forth above.

Claims 17 and 24 remain rejected because the specification does not provide a nexus between the disruption in LRP5 and the phenotypes of retinal degeneration, increased anxiety or hypoactivity. Applicants have not addressed this portion of the rejection.

New matter

Claims 17-19, 24 and 26-30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The rejection of claims 17 and 24 regarding a mouse having a disruption in LRP5 that is hypoactivity has been withdrawn. Support is found on pg 51, lines 6-8.

The phrase "null LRP5 allele" in claim 26, et al., is new matter. Support has not been provided for the amendment and none can be found in the specification as originally filed. The phrases "null allele" and "LRP5 allele" cannot be found and raise indefinite rejections (see 112/2nd below).

A "null LRP5 allele... ...comprising exogenous DNA" in claim 26 is new matter. Support has not been provided for the amendment and none can be found in the specification as originally filed. The specification does not contemplate introducing any "exogenous DNA" as broadly claimed to disrupt the GABA-B1A gene.

The breadth of "selection marker" in claim 27 is new matter. Support cannot be found on the specification, Examples, Figures or claims as originally filed.

The limitation of "PGK-neo fusion gene having two lacO sites" in claim 29 is new matter. Support cannot be found on pg 9, lines 17-20, pg 19, line 17, through pg 121, line 5, the Examples, Figures or claims as originally filed.

Indefiniteness

Claims 17-19, 24 and 26-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

For clarity, the term "LRP5 allele" in claim 26 is definite. The term "LRP5 gene" is defined in the specification as "a comprising [sic] SEQ ID NO:1 or comprising the sequence identified in Genebank as Accession No. NM_008513; G1:6678715. In one aspect, the coding sequence of the LPR5 gene comprises SEQ ID NO:1 or comprises the gene identified in Genebank as Accession No. NM_008513; G1:6678715" (pg 6, lines 11-15). An allele is defined as "one of a variant form of a gene at a particular locus, or location on a chromosome. Different alleles produce variation in inherited characteristics such as hairy color or blood type" (definition of "allele" from genome.gov). Therefore, the term LRP5 allele encompasses SEQ ID NO:1, the sequence identified in Genebank as Accession No. NM_008513; G1:6678715 or alleles thereof.

The metes and bounds of a "null LRP5 allele" in claim 26 are indefinite. It is unclear if the phrase is limited to a mouse without any of the LRP5 gene, or if the phrase encompasses a mouse without any of the coding region of the LRP5 gene, a mouse with a disruption in the LRP5 gene, wherein said disruption does not allow production of functional LRP5, or a mouse with a disruption in the LRP5 gene, wherein said disruption causes less than normal amounts of functional LRP5. The metes and bounds of what applicants consider a "null" allele cannot be determined.

Claim Rejections - 35 USC § 102

New claims 26-28 and 30 are rejected and claim 24 as amended is rejected under 35 U.S.C. 102(b) as being anticipated by Rohlmann (Nature Biotech., Nov. 1996, Vol. 14, pg 1562-1565) or Rohlmann (1998, J. Clin. Invest., Vol. 101, pg 689-695).

Rohlmann (1996) taught making a transgenic mouse having a disruption in LRP using a construct with the neo gene inserted into the LRP gene transfected into ES cells (pg 1652, col. 2, "Generation of $LRP^{flox/flox}$"; pg 1653, col. 2, Fig. 1A). The patent office does not have the ability to analyze the mouse described by Rohlmann to determine how the LRP gene disrupted by Rohlmann correlates to the LRP5 gene claimed. Therefore, without evidence to the contrary, the LRP gene disrupted by Rohlmann was inherently the LRP5 gene as claimed because it had the same structure as SEQ ID NO:1 or comprised SEQ ID NO:1 and encoded SEQ ID NO:2.

Rohlmann (1998) has been included because it also describes the mouse made by Rohlmann in 1996.

Claims 17-19 have not been included because Rohlmann (1996) and Rohlmann (1998) did not teach the mouse had "retinal degeneration, increased anxiety or hypoactivity" as claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 24, 26-28 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rohlmann (Nature Biotech., Nov. 1996, Vol. 14, pg 1562-1565) in view of Hey (1998, Gene, Vol. 216, pg 103-111).

Rohlmann (1996) taught making a transgenic mouse having a disruption in LRP using a construct with the neo gene inserted into the LRP gene transfected into ES cells (pg 1652, col. 2, "Generation of $LRP^{flox/flox}$"; pg 1653, col. 2, Fig. 1A). Rohlmann did not teach the LRP gene encoded for the amino acid sequence of SEQ ID NO:2.

However, Hey taught the amino acid sequence of the mouse LRP5 protein, SEQ ID NO:2 (pg 107).

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to make a transgenic mouse having a disruption in LRP as taught by Rohlmann wherein the LRP was LRP5 as taught by Hey. One of ordinary skill in the art at the time the invention was made would have been motivated to disrupt the LRP5 gene described by Hey instead of the LRP gene described by Rohlmann to gain clues as to the function of the LRP5 gene in vivo, specifically the liver. In fact, the LRP gene described by Rohlmann may have been the LRP5 gene because both were expressed in the liver (Hey, pg 108, ¶ bridging 1-2, Fig. 5A, lane 5; Rohlmann, pg 689, last ¶).

Thus, Applicants' claimed invention as a whole is *prima facie* obvious in the absence of evidence to the contrary.

Claims 24 and 26-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Signorini (1997, PNAS, Vol. 94, pg 923-927) in view of Hey (1998, Gene, Vol. 216, pg 103-111).

Signorini taught making a transgenic mouse having a heterozygous or homozygous disruption in an inward rectifier protein (GIRK2/Kir3.2). The disruption comprised DNA cassette encoding PGK and neomycin which was visible using PCR (pg 924, col. 2, 2nd ¶; caption to Fig. 1 on pg 924). Signorini did not teach disrupting the LRP5 gene in the mice.

However, Hey taught the nucleic acid sequence encoding SEQ ID NO:2.

Thus, it would have been obvious to one of ordinary skill in the art at the time the

invention was made to make a transgenic mouse having a disruption in a protein as taught by Signorini wherein the protein was LRP5 as taught by Hey. One of ordinary skill in the art at the time the invention was made would have been motivated to disrupt the LRP5 gene instead of the Kir3.2 gene to determine the function of LRP5 *in vivo*.

Thus, Applicants' claimed invention, as a whole is prima facie obvious in the absence of evidence to the contrary.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Weaver of record (J. Biol. Chem., May 30, 1997, Vol. 272, No. 22, pg 14372-14379) taught cells with a deletion in LRP but did not teach mice with a deletion in LRP.

Kim (J. Biochem., 1998, Vol. 124, pg 1072-1076) described the human and rabbit LRP5 genes, which was expressed in the liver.

Pinson (Nature, Sept. 28, 2000, Vol. 407, pg 535-538) made a transgenic mouse having a disruption in LRP6 using a trap vector transfected into ES cells (pg 538, col. 1, 1st full ¶). The LRP6 gene described by Pinson is not an LRP5 allele as claimed because it is not an LRP5 gene or a variant form of the LRP5 gene at the LRP5 locus on the chromosome. While LRP6 may have homology with LRP5, LRP6 is not an LRP5 allele as claimed.

Fujino (PNAS, Jan. 7, 2003, Vol. 100, No. 1, pg 229-234).

Jiao (Am. J. Human. Genetics, 2004, Vol. 75, pg 878-884).

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached at the office on Monday, Tuesday, Thursday and Friday from 9:30 am to 6:00 pm at 571-272-0738.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within

5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on 571-272-0735.

The official fax number for this Group is (571) 273-8300.

Michael C. Wilson

MICHAEL WILSON
PRIMARY EXAMINER